

# SEQUENCE LISTING

<110> Tang, Jordan J.N.  
Hong, Lin  
Ghosh, Arun K.

<120> Inhibitors of Memapsin 2 and Use Thereof

<130> OMRF 182

<140> Not Yet Assigned

<141> 2000-06-27

<150> 60/141,363

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<150> 60/210,292

<151> 2000-06-08

<160> 31

<170> PatentIn Ver. 2.1

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<212> DNA

<213> Homo sapiens

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<211> 488  
<212> PRT  
<213> Homo sapiens

<220>  
<223> Purified Memapsin 2

<220>  
<223> Amino Acids 28-48 are remnant putative propeptide residues

<220>  
<223> Amino Acids 58-61, 78, 80, 82-83, 116, 118-121, 156, 166, 174, 246, 274, 276, 278-281, 283, and 376-377 are residues in contact with the OM99-2 inhibitor

<220>  
<223> Amino acids 54-57, 61-68, 73-80, 86-89, 109-111, 113-118, 123-134, 143-154, 165-168, 198-202, and 220-224 are N-lobe Beta Strands

<220>  
<223> Amino Acids 184-191 and 210-217 are N-lobe Helices

<220>  
<223> Amino acids 237-240, 247-249, 251-256, 259-260, 273-275, 282-285, 316-318, 331-336, 342-348, 354-357, 366-370, 372-375, 380-383, 390-395, 400-405, and 418-420 are C-lobe Beta Strands

<220>  
<223> Amino Acids 286-299, 307-310, 350-353, 384-387, and 427-431 are C-lobe Helices

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Leu Arg Ser Gly Leu Gly Gly Ala Pro Leu Gly Leu Arg Leu Pro Arg  
20 25 30  
Glu Thr Asp Glu Glu Pro Glu Glu Pro Gly Arg Arg Gly Ser Phe Val  
35 40 45  
Glu Met Val Asp Asn Leu Arg Gly Lys Ser Gly Gln Gly Tyr Tyr Val  
50 55 60

Glu	Met	Thr	Val	Gly	Ser	Pro	Pro	Gln	Thr	Leu	Asn	Ile	Leu	Val	Asp	
65					70					75					80	
Thr	Gly	Ser	Ser	Asn	Phe	Ala	Val	Gly	Ala	Ala	Pro	His	Pro	Phe	Leu	
				85					90					95		
His	Arg	Tyr	Tyr	Gln	Arg	Gln	Leu	Ser	Ser	Thr	Tyr	Arg	Asp	Leu	Arg	
			100					105					110			
Lys	Gly	Val	Tyr	Val	Pro	Tyr	Thr	Gln	Gly	Lys	Trp	Glu	Gly	Glu	Leu	
		115					120					125				
Gly	Thr	Asp	Leu	Val	Ser	Ile	Pro	His	Gly	Pro	Asn	Val	Thr	Val	Arg	
	130					135					140					
Ala	Asn	Ile	Ala	Ala	Ile	Thr	Glu	Ser	Asp	Lys	Phe	Phe	Ile	Asn	Gly	
145					150					155					160	
Ser	Asn	Trp	Glu	Gly	Ile	Leu	Gly	Leu	Ala	Tyr	Ala	Glu	Ile	Ala	Arg	
			165					170						175		
Pro	Asp	Asp	Ser	Leu	Glu	Pro	Phe	Phe	Asp	Ser	Leu	Val	Lys	Gln	Thr	
		180					185						190			
His	Val	Pro	Asn	Leu	Phe	Ser	Leu	Gln	Leu	Cys	Gly	Ala	Gly	Phe	Pro	
		195					200					205				
Leu	Asn	Gln	Ser	Glu	Val	Leu	Ala	Ser	Val	Gly	Gly	Ser	Met	Ile	Ile	
	210					215					220					
Gly	Gly	Ile	Asp	His	Ser	Leu	Tyr	Thr	Gly	Ser	Leu	Trp	Tyr	Thr	Pro	
225					230					235					240	
Ile	Arg	Arg	Glu	Trp	Tyr	Tyr	Glu	Val	Ile	Ile	Val	Arg	Val	Glu	Ile	
			245					250						255		
Asn	Gly	Gln	Asp	Leu	Lys	Met	Asp	Cys	Lys	Glu	Tyr	Asn	Tyr	Asp	Lys	
		260						265					270			
Ser	Ile	Val	Asp	Ser	Gly	Thr	Thr	Asn	Leu	Arg	Leu	Pro	Lys	Lys	Val	
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Phe	Glu	Ala	Ala	Val	Lys	Ser	Ile	Lys	Ala	Ala	Ser	Ser	Thr	Glu	Lys	
	290					295					300					
Phe	Pro	Asp	Gly	Phe	Trp	Leu	Gly	Glu	Gln	Leu	Val	Cys	Trp	Gln	Ala	
305					310				315						320	

Gly Thr Thr Pro Trp Asn Ile Phe Pro Val Ile Ser Leu Tyr Leu Met  
 325 330 335

Gly Glu Val Thr Asn Gln Ser Phe Arg Ile Thr Ile Leu Pro Gln Gln  
 340 345 350

Tyr Leu Arg Pro Val Glu Asp Val Ala Thr Ser Gln Asp Asp Cys Tyr  
 355 360 365

Lys Phe Ala Ile Ser Gln Ser Ser Thr Gly Thr Val Met Gly Ala Val  
 370 375 380

Ile Met Glu Gly Phe Tyr Val Val Phe Asp Arg Ala Arg Lys Arg Ile  
 385 390 395 400

Gly Phe Ala Val Ser Ala Cys His Val His Asp Glu Phe Arg Thr Ala  
 405 410 415

Ala Val Glu Gly Pro Phe Val Thr Leu Asp Met Glu Asp Cys Gly Tyr  
 420 425 430

Asn Ile Pro Gln Thr Asp Glu Ser Thr Leu Met Thr Ile Ala Tyr Val  
 435 440 445

Met Ala Ala Ile Cys Ala Leu Phe Met Leu Pro Leu Cys Leu Met Val  
 450 455 460

Cys Gln Trp Arg Cys Leu Arg Cys Leu Arg Gln Gln His Asp Asp Phe  
 465 470 475 480

Ala Asp Asp Ile Ser Leu Leu Lys  
 485

<210> 3  
 <211> 503  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <223> Pro-memapsin 2

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 <223> Amino Acids 1-15 are vector-derived residues

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 <223> Amino Acids 16-64 are a putative pro peptide

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<223> Amino Acids 1-13 are the T7 promoter

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<223> Amino Acids 16-456 are Pro-memapsin 2-T1

<220>

<223> Amino Acids 16-421 are Promemapsin 2-T2.

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Gly Val Leu Pro Ala His Gly Thr Gln His Gly Ile Arg Leu Pro Leu  
20 25 30

Arg Ser Gly Leu Gly Gly Ala Pro Leu Gly Leu Arg Leu Pro Arg Glu  
35 40 45

Thr Asp Glu Glu Pro Glu Glu Pro Gly Arg Arg Gly Ser Phe Val Glu  
50 55 60

Met Val Asp Asn Leu Arg Gly Lys Ser Gly Gln Gly Tyr Tyr Val Glu  
65 70 75 80

Met Thr Val Gly Ser Pro Pro Gln Thr Leu Asn Ile Leu Val Asp Thr  
85 90 95

Gly Ser Ser Asn Phe Ala Val Gly Ala Ala Pro His Pro Phe Leu His  
100 105 110

Arg Tyr Tyr Gln Arg Gln Leu Ser Ser Thr Tyr Arg Asp Leu Arg Lys  
115 120 125

Gly Val Tyr Val Pro Tyr Thr Gln Gly Lys Trp Glu Gly Glu Leu Gly  
130 135 140

Thr Asp Leu Val Ser Ile Pro His Gly Pro Asn Val Thr Val Arg Ala  
145 150 155 160

Asn Ile Ala Ala Ile Thr Glu Ser Asp Lys Phe Phe Ile Asn Gly Ser  
165 170 175

Asn Trp Glu Gly Ile Leu Gly Leu Ala Tyr Ala Glu Ile Ala Arg Pro  
180 185 190

Asp Asp Ser Leu Glu Pro Phe Phe Asp Ser Leu Val Lys Gln Thr His  
195 200 205

Val Pro Asn Leu Phe Ser Leu Gln Leu Cys Gly Ala Gly Phe Pro Leu  
 210 215 220

Asn Gln Ser Glu Val Leu Ala Ser Val Gly Gly Ser Met Ile Ile Gly  
 225 230 235 240

Gly Ile Asp His Ser Leu Tyr Thr Gly Ser Leu Trp Tyr Thr Pro Ile  
 245 250 255

Arg Arg Glu Trp Tyr Tyr Glu Val Ile Ile Val Arg Val Glu Ile Asn  
 260 265 270

Gly Gln Asp Leu Lys Met Asp Cys Lys Glu Tyr Asn Tyr Asp Lys Ser  
 275 280 285

Ile Val Asp Ser Gly Thr Thr Asn Leu Arg Leu Pro Lys Lys Val Phe  
 290 295 300

Glu Ala Ala Val Lys Ser Ile Lys Ala Ala Ser Ser Thr Glu Lys Phe  
 305 310 315 320

Pro Asp Gly Phe Trp Leu Gly Glu Gln Leu Val Cys Trp Gln Ala Gly  
 325 330 335

Thr Thr Pro Trp Asn Ile Phe Pro Val Ile Ser Leu Tyr Leu Met Gly  
 340 345 350

Glu Val Thr Asn Gln Ser Phe Arg Ile Thr Ile Leu Pro Gln Gln Tyr  
 355 360 365

Leu Arg Pro Val Glu Asp Val Ala Thr Ser Gln Asp Asp Cys Tyr Lys  
 370 375 380

Phe Ala Ile Ser Gln Ser Ser Thr Gly Thr Val Met Gly Ala Val Ile  
 385 390 395 400

Met Glu Gly Phe Tyr Val Val Phe Asp Arg Ala Arg Lys Arg Ile Gly  
 405 410 415

Phe Ala Val Ser Ala Cys His Val His Asp Glu Phe Arg Thr Ala Ala  
 420 425 430

Val Glu Gly Pro Phe Val Thr Leu Asp Met Glu Asp Cys Gly Tyr Asn  
 435 440 445

Ile Pro Gln Thr Asp Glu Ser Thr Leu Met Thr Ile Ala Tyr Val Met  
 450 455 460

Ala Ala Ile Cys Ala Leu Phe Met Leu Pro Leu Cys Leu Met Val Cys  
465 470 475 480

Gln Trp Arg Cys Leu Arg Cys Leu Arg Gln Gln His Asp Asp Phe Ala  
485 490 495

Asp Asp Ile Ser Leu Leu Lys  
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<210> 4  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 4  
Ser Glu Val Lys Met Asp Ala Glu Phe Arg  
1 5 10

<210> 5  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Synthetic  
Peptide

<400> 5  
Ser Glu Val Asn Leu Asp Ala Glu Phe Arg  
1 5 10

<210> 6  
<211> 8  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Synthetic  
Peptide

<400> 6



Ser Val Asn Met Ala Glu Gly Asp

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5

<210> 7

<211> 12

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic  
Peptide

<400> 7

Lys Gly Gly Val Val Ile Ala Thr Val Ile Val Lys

1

5

10

<210> 8

<211> 4

<212> PRT

<213> Homo sapiens

<400> 8

Asp Thr Ser Gly

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<210> 9

<211> 8

<212> PRT

<213> Homo sapiens

<400> 9

Leu Val Asn Met Ala Glu Gly Asp

1

5

<210> 10

<211> 28

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 10

ggtaagcatc ccccatggcc ccaacgtc

28

<210> 11  
<211> 28  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 11  
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<210> 12  
<211> 34  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

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acgttgtctt tgatcgggcc cgaaaacgaa ttgg

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<210> 13  
<211> 33  
<212> DNA  
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<220>  
<223> Description of Artificial Sequence: Primer

<400> 13  
ccaattcggtt ttcggggccg atcaaagaca acg

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<210> 14  
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<212> DNA  
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<223> Description of Artificial Sequence: Primer

<400> 14  
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<210> 15  
<211> 23  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 15  
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23

<210> 16  
<211> 26  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 16  
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26

<210> 17  
<211> 31  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 17  
gaggtggcctt atgagtattt cttccagggt a

31

<210> 18  
<211> 22  
<212> DNA  
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<223> Description of Artificial Sequence: Primer

<400> 18  
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22

<210> 19  
<211> 24  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 19  
tgacaccaga ccaactggta atgg

24

<210> 20  
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<212> DNA  
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<220>  
<223> Description of Artificial Sequence: Primer

<400> 20  
catatggcgg gagtgctgcc tgcccac

27

<210> 21  
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<212> DNA  
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<220>  
<223> Description of Artificial Sequence: Primer

<400> 21  
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<210> 22  
<211> 8  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Oxidized  
Insulin B-chain

<220>

<223> Xaa at site 3 represents cysteic acid

<400> 22

His Leu Xaa Gly Ser His Leu Val

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5

<210> 23

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Oxidized  
Insulin B-chain

<220>

<223> Xaa at site 1 represents cysteic acid

<400> 23

Xaa Gly Glu Arg Gly Phe Phe Tyr

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5

<210> 24

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic  
Peptide

<400> 24

Val Gly Ser Gly Val

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5

<210> 25

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic  
Peptide

<400> 25

Val Gly Ser Gly Val Leu Leu  
1 5

<210> 26

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic  
Peptide

<400> 26

Gly Val Leu Leu Ser Arg Lys  
1 5

<210> 27

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Inhibitors

<400> 27

Val Asn Leu Ala Ala Glu Phe  
1 5

<210> 28

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Inhibitors

<400> 28

Glu Val Asn Leu Ala Ala Glu Phe  
1 5

<210> 29

<211> 4

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic Peptide

<400> 29

Asn Leu Ala Ala

1

<210> 30

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic Peptide

<400> 30

Val Gly Ser Gly Val Leu Leu Ser Arg Lys

1

5

10

<210> 31

<211> 326

<212> PRT

<213> Homo sapiens

<220>

<223> Amino acids 2-5, 6-9, 13-20, 25-32, 65-67, 69-74, 79-87, 89-91, 99-106, 119-122, 150-154, 164-167, 180-183, 191-194, 196-199, 201-204, 210-214, 221-223, 258-262, 265-269, and 275-278 are Beta Strands

<220>

<223> Amino acids 281-284, 286-288, 298-301, 310-315, and 319-324 are Beta strands

<220>

<223> Amino acids 48-51, 111-114, 136-142, 225-234, 249-254, 271-274, and 303-306 are Helices

<220>

<223> Amino acids 12-13, 30, 32, 34-35, 73-77, 111, 117, 120, 189, 213, 215, 217-220, 287, 289, 291, 298, and 300 are residues in contact with pepstatin.

<220>

<223> Pepsin

<400> 31

Val Asp Glu Gln Pro Leu Glu Asn Tyr Leu Asp Met Glu Tyr Phe Gly  
1 5 10 15

Thr Ile Gly Ile Gly Thr Pro Ala Gln Asp Phe Thr Val Val Phe Asp  
20 25 30

Thr Gly Ser Ser Asn Leu Trp Val Pro Ser Val Tyr Cys Ser Ser Leu  
35 40 45

Ala Cys Thr Asn His Asn Arg Phe Asn Pro Glu Asp Ser Ser Thr Tyr  
50 55 60

Gln Ser Thr Ser Glu Thr Val Ser Ile Thr Tyr Gly Thr Gly Ser Met  
65 70 75 80

Thr Gly Ile Leu Gly Tyr Asp Thr Val Gln Val Gly Gly Ile Ser Asp  
85 90 95

Thr Asn Gln Ile Phe Gly Leu Ser Glu Thr Glu Pro Gly Ser Phe Leu  
100 105 110

Tyr Tyr Ala Pro Phe Asp Gly Ile Leu Gly Leu Ala Tyr Pro Ser Ile  
115 120 125

Ser Ser Ser Gly Ala Thr Pro Val Phe Asp Asn Ile Trp Asn Gln Gly  
130 135 140

Leu Val Ser Gln Asp Leu Phe Ser Val Tyr Leu Ser Ala Asp Asp Gln  
145 150 155 160

Ser Gly Ser Val Val Ile Phe Gly Gly Ile Asp Ser Ser Tyr Tyr Thr  
165 170 175

Gly Ser Leu Asn Trp Val Pro Val Thr Val Glu Gly Tyr Trp Gln Ile  
180 185 190

Thr Val Asp Ser Ile Thr Met Asn Gly Glu Ala Ile Ala Cys Ala Glu  
195 200 205

Gly Cys Gln Ala Ile Val Asp Thr Gly Thr Ser Leu Leu Thr Gly Pro  
210 215 220

Thr Ser Pro Ile Ala Asn Ile Gln Ser Asp Ile Gly Ala Ser Glu Asn



225		230		235		240
Ser Asp Gly Asp Met Val Val Ser Cys Ser Ala Ile Ser Ser Leu Pro						
	245		250		255	
Asp Ile Val Phe Thr Ile Asn Gly Val Gln Tyr Pro Val Pro Pro Ser						
	260		265		270	
Ala Tyr Ile Leu Gln Ser Glu Gly Ser Cys Ile Ser Gly Phe Gln Gly						
	275		280		285	
Met Asn Leu Pro Thr Glu Ser Gly Glu Leu Trp Ile Leu Gly Asp Val						
	290		295		300	
Phe Ile Arg Gln Tyr Phe Thr Val Phe Asp Arg Ala Asn Asn Gln Val						
305		310		315		320
Gly Leu Ala Pro Val Ala						
	325					